

Application No. 09/920,435  
Filed: August 1, 2001  
TC Art Unit: 1639  
Confirmation No.: 6450

REMARKS

Claims 1-14, 21 and 22 are pending in the present application. The Examiner has rejected claims 1-14, 21 and 22 under 35 U.S.C. § 103 as obvious based on a combination of journal articles to Kaur et al. and van Breemen et al. Applicants respectfully request reconsideration and withdrawal of the rejections by the Examiner based on the remarks presented herein.

Claim Rejections 35 U.S.C. § 103

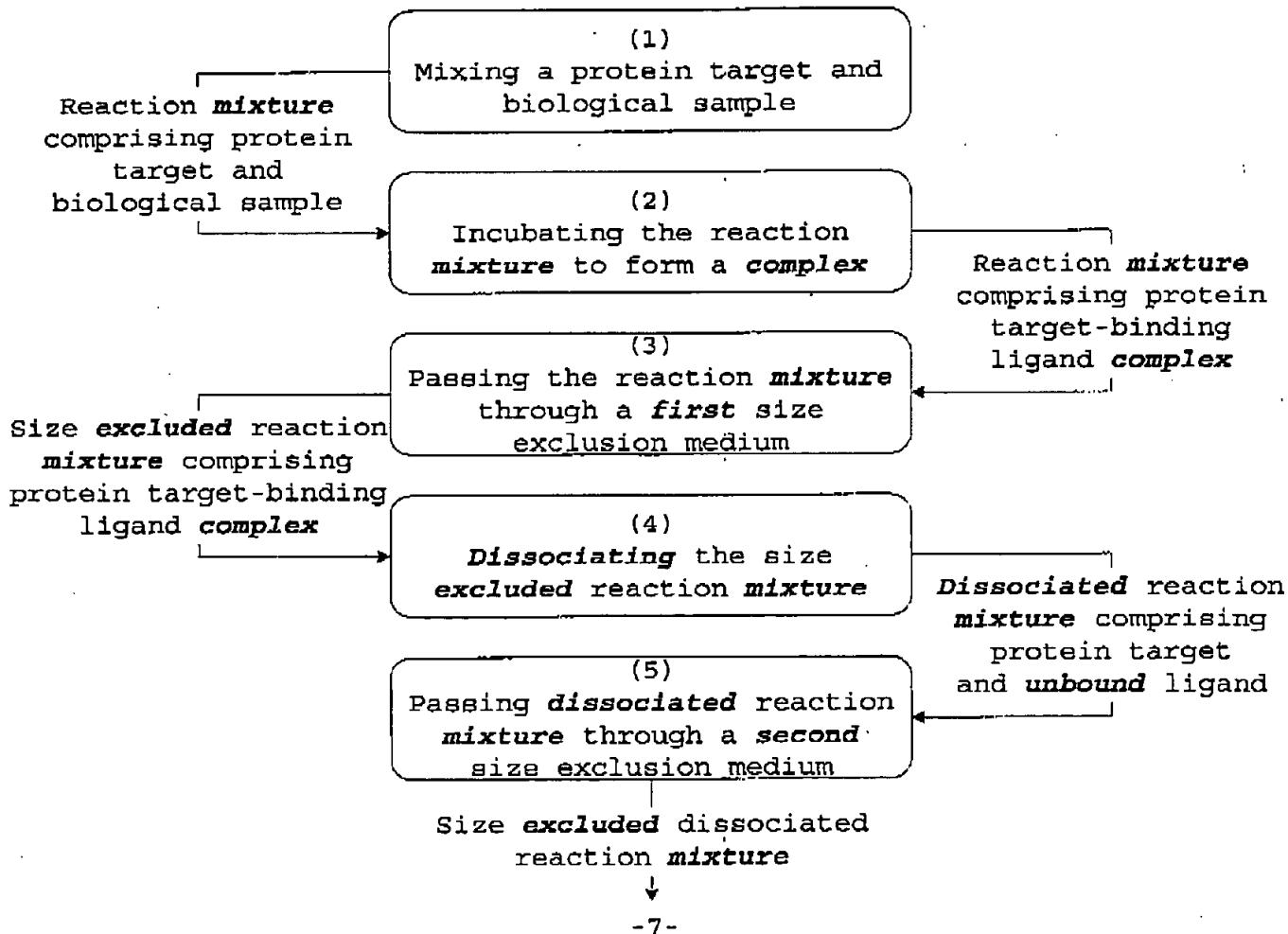
The Examiner has rejected claims 1-14, 21 and 22 as obvious based on a combination of journal articles to Kaur et al. and van Breemen et al. The Examiner has asserted that Kaur et al. teach each of the limitations of the claimed method without reference to a second size exclusion medium as required by the pending claims. The Examiner has contended that van Breemen et al. disclose pulsed ultrafiltration-mass spectrometry that can be used as a substitute for the mass spectrometry of Kaur et al. such that a combination of the references provides a second size exclusion medium. Applicants respectfully disagree with the contentions of the Examiner and the characterizations of the teachings in Kaur et al. and van Breemen et al. Applicants particularly submit that van Breemen et al. do not teach pulsed ultrafiltration-mass spectrometry that acts as a second size exclusion medium.

Applicants indicate that van Breemen et al. suggest pulsed ultrafiltration-mass spectrometry in which ultrafiltration of a ligand-receptor **complex** is performed. The ultrafiltration taught by van Breemen et al. also occurs **prior** to any **dissociation** of the ligand-receptor **complex**. A teaching that discloses performing ultrafiltration of a **complex** prior to its **dissociation** cannot be

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applied to render the second size exclusion medium limitation of the claimed method obvious. Applicants also contend that such a teaching cannot be properly combined with Kaur et al. to establish a *prima facie* basis for the obviousness of the pending claims.

Applicants maintain that the claimed method requires passing a reaction mixture or *complex* through a *first* size exclusion medium and subjecting the size excluded reaction mixture to *dissociation* prior to passing the dissociated mixture through a *second* size exclusion medium. A diagram of the claimed method underscores the breadth of the pending claims.



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The diagram clearly indicates a method in which a protein target-binding ligand **complex** is introduced to (3) a **first** size exclusion medium. The **first** size exclusion medium operates to **exclude** material that does not comprise the **complex**. The **complex** is thereafter (4) **dissociated** to comprise the protein target and **unbound** ligand. The **dissociated** protein target and **unbound** ligand are subjected to (5) a **second** size exclusion medium that **excludes** molecules that are larger than a preset value. The diagram also identifies the yield or product from performing each of the stages and providing such to a latter stage.

In comparison, the journal article to van Breemen et al. teaches separating a ligand-receptor **complex** from unbound material by ultrafiltration and **dissociating** the isolated **complex** after the separation. The **dissociated** complex is then passed onto a mass spectrometer. The article does not mention an **exclusion** or separation of the **dissociated** mixture comprising the receptor and unbound ligand. The journal article also does not disclose **isolating** molecules in the **dissociated** receptor and **unbound** ligand mixture prior to analysis via a mass spectrometer or related method. Thus, an individual of ordinary skill in the art would understand that combining the teachings of Kaur et al. with van Breemen et al. cannot render the claimed method obvious.

Applicants have identified the specific teachings in van Breemen et al. that elucidate a proper interpretation of the journal article to assist in examination of the application.

Journal Article Disclosure	Journal Article Citation
Ligand-receptor <b>complexes</b> were purified by <b>ultrafiltration</b> and	First paragraph of page 2159 at approximately line 10 in column 1

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then **dissociated** using methanol with emphasis added to elute the ligands

Based on an extension of our method for pulse **ultrafiltration** measurement of affinity constants for ligand-receptor **bonding**

A preliminary report on the use of pulsed **ultrafiltration** mass spectrometry for the measurement of classical equilibrium **binding** constants

The mobile phase was changed to methanol-water to **dissociate** the enzyme-ligand **complex** and thereby release the bound ligands for identification by electrospray mass spectroscopy

**Bound** ligands were eluted into the mass spectrometer

**Bound** EHNA was released into the mass spectrometer by eluting the [ultrafiltration] chamber using methanol in water

During pulsed ultrafiltration, ligand-receptor **complexes** remain in solution in the chamber while unbound compound are washed away

The ligand-receptor **complex** is

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disrupted so that the ligands are approximately line 36 in column 1 released to the mass spectrometer with emphasis added

After infusion of a dilution solution of the compounds through a ultrafiltration chamber bound ligands were released into the mass spectrometer

First paragraph of page 2162 at approximately line 3 in column 1 with emphasis added

Methanol was introduced into the mobile phase to dissociate the enzyme-ligand complex and release bound ligands for identification by electrospray mass spectrometry

Second paragraph of page 2162 at approximately line 15 in column 1 with emphasis added

The teachings clearly evidence that van Breemen et al. discloses ultrafiltration methods that are used to exclude ligand-receptor complexes from unbound material. The journal article does not suggest performing an ultrafiltration or exclusion of a complex that has been dissociated into a receptor and an unbound ligand as required by the claimed method.

An individual of ordinary skill in the art would only be motivated to substitute the first size exclusion medium disclosed by Kaur et al. with the ultrafiltration method taught by van Breemen et al. This substitution is practical as the first size exclusion medium described in Kaur et al. is specifically used to exclude ligand-receptor complexes from unbound material just as the ultrafiltration disclosure of van Breemen et al. A motivation is not present that would suggest to an individual within the art to use the ultrafiltration method of van Breemen et al. to separate a dissociated mixture comprising a receptor and an

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**unbound** ligand as the journal article is entirely unrelated to excluding molecules from a **dissociated** receptor and **unbound** ligand mixture prior to analysis via a mass spectrometry or related method.

The patent laws require that each limitation of the claims under consideration be disclosed in a reference(s) in order to establish a *prima facie* basis for obviousness. Applicants have demonstrated that a combination of the cited journal articles does not describe using a **second** size exclusion medium to exclude a **complex** that has been **dissociated** into a receptor and an **unbound** ligand as required by the claimed method. The journal articles plainly do not disclose a limitation regarding a **second** size medium. The articles also do not teach each of the limitations of the method as arranged in the pending claims. The pending claims particularly require **dissociation** of the protein-target binding ligand complex **prior** to subjecting the dissociated mixture to a **second** size exclusion medium. The arrangement of limitations recited in the claimed method are provided to perform the invention. The journal articles cited by the Examiner are not capable of performing the invention as arranged in the claims.

The patent laws have also settled that a reference(s) cannot be interpreted in a manner that would obviate the advantages that it discloses or teaches. Applicants contend that the Examiner has not fully considered the advantages of pulsed ultrafiltration-mass spectrometry as suggested by van Breemen et al. The journal article to van Breemen et al. distinctly characterizes the advantages of performing ultrafiltration of ligand-receptor **complexes** then **dissociating** the excluded complexes **prior** to analysis via a mass spectrometer. These advantages also

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underscore the experimental concepts presented by van Breemen et al. The Examiner has avoided the plain teachings of these advantages in applying van Breemen et al. to render the claimed method obvious.

In summary, the claimed method requires a **second** size exclusion medium to exclude a **complex** that has been **dissociated** into a receptor and an **unbound** ligand. The journals articles to Kaur et al. and van Breemen et al. each disclose subjecting a ligand-receptor **complex** to a size exclusion medium to exclude unbound material and then **dissociating** the complexes **prior** to analysis via a mass spectrometer. The articles do not suggest or mention using a **second** size exclusion medium that would **exclude** molecules that are present in the **dissociated** receptor and **unbound** ligand mixture prior to an analysis via a mass spectrometer or related method. Thus, Applicants submit that the rejections by the Examiner have been overcome as claims 1-14, 21 and 22 are not obvious based on Kaur et al. in view of van Breemen et al.

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CONCLUSION

Based on the remarks presented herein, reconsideration and withdrawal of the rejections by the Examiner and allowance of the application with the pending claims are respectfully requested.

The Examiner is encouraged to telephone the undersigned attorney to discuss any matter that would expedite allowance of the present application.

Respectfully submitted,

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